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(54) Title: HUMAN JTV1 GENE OVERLAPS PMS2 GENE

(57) Abstract

The hPMS2 gene encodes a protein which is involved in DNA mismatch repair and is mutated in a subset of patients with hereditary nonpolyposis colon cancer (HNPCC). The previously published hPMS2 cDNA sequence lacks an upstream in-frame stop codon preceding the presumptive initiating methionine. To further evaluate the 5' terminus of the hPMS2 coding region, we isolated additional cDNA clones, RT-PCR products, and the corresponding 5' genomic segment of the hPMS2 locus. The hPMS2 gene transcripts were found to have heterogeneous but collinear 5' termini, one of which contained an in-frame termination codon preceding the initiating methionine. In addition, a gene encoding a 34.5 kDa polypeptide was found to transcriptionally initiate within hPMS2 from the opposite strand.

peptides from the 85 kDa protein revealed it to be the product of *hMLH1*, and this protein's molecular weight agreed with that predicted from the cDNA sequence (Bronner et.al., 1994; Papadopoulos et.al., 1994). The sequence of the peptide generated from the 110 kDa component showed it to be similar to the *hPMS2* mutL-homolog; however, the predicted molecular weight of *hPMS2* is only 95 kDa (Nicolaides, et.al., 1994). Since the previously isolated *hPMS2* cDNA clones lacked an in-frame termination codon upstream of the presumptive initiating methionine, it was possible that the open reading frame extended further upstream. Thus there is a need in the art for further knowledge of the genetic structures of and adjacent to the known *hPMS2* gene.

SUMMARY OF THE INVENTION

It is an object of the invention to provide a novel, isolated, human gene on chromosome 7.

It is an object of the invention to provide vectors and host cells for making a novel human gene product.

It is another object of the invention to provide compositions of matter containing the human gene product.

These and other objects are provided by one or more of the embodiments described below. In one embodiment of the invention, a segment of cDNA is provided. The cDNA consists of the sequence of nucleotides shown in Figure 2.

According to another embodiment of the invention, a vector comprising the segment of cDNA which consists of the sequence of nucleotides shown in Figure 2 is provided, as well as host cells comprising the vector.

According to still another embodiment of the invention, a composition is provided. The composition consists essentially of a protein consisting of the amino acid sequence shown in Figure 2

In yet another embodiment of the invention a composition of protein *JTV1* as shown in Figure 1 is provided. The composition is free of other human proteins.

In another embodiment of the invention a segment of cDNA is provided which segment encodes the amino acid sequence of JTV1 protein shown in Figure 2.

cDNA probes are also provided by the present invention. The cDNA portion of said probes consists of between 15 and 1176 contiguous nucleotides of the sequence shown in SEQ ID NO:1.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the sequence of the 5' region of *hPMS2* and predicted coding region. The arrow indicates the 5' end of the previously published cDNA clone. The presumptive initiating methionine is underlined.

Figure 2 shows the sequence of *JTV1*. The sequence has been deposited in Genbank, accession number U24169. The presumptive initiating methionine is underlined.

Figure 3 demonstrates the genomic localization of *JTV1*. The genomic localization of *hPMS2* and *JTV1* were confirmed by screening somatic-cell hybrids containing various regions of human chromosome 7. Lane 1, GM10791 contains entire chromosome 7 in a chinese hamster ovary (CHO) background; lane 2, NA11440 contains 7pter>7p22 in a CHO background; lane 3, Ru-Rag4-13 contains 7cen-7pter in a murine background; lane 4, 4AF1/106/K015 contains 7cen-qter in a murine background; lane 5, GM05184.17 contains 7q21.2-qter in a CHO background; lane 6, 2068Rag22-2 contains 7q22-qter in a murine background; lane 7, human genomic DNA; lane 8, mouse genomic DNA; lane 9, CHO genomic DNA.

Figure 4 demonstrates the mapping of transcriptional start sites of *hPMS2* and *JTV1*. Sequence of the genomic region containing the 5' ends of the two genes is shown. The sequence is numbered in respect to codon 1 of *hPMS2*. Lower case letters denote intronic sequence of *JTV1* (from nt -479 to -833) and *hPMS2* (from +24 to +108). Arrows indicate the 5' ends of *hPMS2* (sense strand) and of *JTV1* (antisense strand) cDNA clones. The underlined ATG codons indicate the predicted initiating methionines for *hPMS2* (at nt +1 on the sense

strand) and *JTV1* (at nt -345 on the antisense strand). The sequence has been deposited in Genbank, accession number U24168.

Figure 5 shows the expression of *hPMS2* and *JTV1*. RNA from various tissues was incubated with reverse transcriptase (RT+) or in control reactions without reverse transcriptase (RT-). The cDNA was used as template for PCR with primers specific for *hPMS2* (A) and *JTV1* (B). RT-PCR products were separated by polyacrylamide gel electrophoresis.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

To investigate the upstream region from *hPMS2*, we isolated additional cDNA clones, analyzed the 5' end of *hPMS2* transcripts with PCR-based techniques, and cloned the corresponding genomic segments. In addition to clarifying the transcript, we serendipitously discovered a previously undescribed gene overlapping *hPMS2*. That gene is termed herein *JTV1*. The sequences of the *JTV1* cDNA and protein are shown in SEQ ID NOS:1 and 2, respectively.

A segment of cDNA according to the present invention refers to a contiguous stretch of deoxyribonucleotides which have a sequence as obtained upon reverse transcriptase of an RNA transcript. Such segments do not contain introns. The segment may be an isolated molecule or it can be covalently joined to other nucleic acid sequences. The segment may, for example, be replicated as part of a vector, such as a plasmid, virus, or minichromosome. The vector may be replicated within a host cell, such as a cell transformed by a recombinant DNA molecule. The host cell may be used to produce JTV1 protein. It can also be used to study regulation of expression of JTV1 sequences, for example by subjecting the host cell to various agents which may or may not affect the expression. Although the DNA sequence is discussed with particularity herein, it is well within the skill of the art to make small mutations, such as single nucleic acid substitutions of one of the other three nucleic acid bases, at any of the positions of the sequence. In addition, it is well within the art to make single base deletions or single base insertions, to study the effect upon protein structure and function.

If JTV1 is produced in a recombinant host cell which is not human, a composition of JTV1 protein will be produced which is free of other human proteins. If JTV1 protein is isolated from naturally producing cells, or from human host cells, then the protein can be purified, for example, using antibodies which are raised against an immunogen comprising JTV1 amino acid sequence. Any other means of purification known in the art can be used, as is desired.

DNA molecules can be made having different nucleotide sequences from that disclosed in SEQ ID NO:1, but which still encode the JTV1 protein as disclosed in SEQ ID NO:2. Using the known coding relationships between codons and amino acids and the disclosed amino acid sequence, numerous other sequences can be readily designed and produced. Such DNA molecules are within the contemplation of the subject invention.

cDNA probes can be used for hybridization studies. Typically they are labeled with a detectable marker, such as a radiolabel or a fluorescent moiety, although they need not be. The cDNA probes of the subject invention consist of at least 15 contiguous nucleotides of the sequence shown in SEQ ID NO:1. If greater specificity is desired, larger molecules of 18, 20, 25, or 30 nucleotides can be used, up to a maximum of the entire sequence of 1176 nucleotides.

JTV1 cDNAs can be used as probes to detect deletions in chromosome 7. Due to the overlapping promoter regions, large deletions of *JTV1* would also be expected to affect *PMS2* expression, leading to Hereditary Non-Polyposis Colorectal Cancer (HNPCC). *JTV1* cDNA can be used in chromosome mapping. It can also be used to assay activity or competence of the *PMS2* promoter region. The presence of *JTV1* transcripts or JTV1 protein suggests that the *PMS2* promoter is intact. If the *PMS2* promoter is intact and *PMS2* products are absent, a structural defect in the coding region is indicated.

JTV1 sequences can be used to guide homologous recombination at the *PMS2* locus. For example, where a *PMS2* mutation is present and therapeutic replacement with a wild-type gene is desired, *PMS2* sequences can be used to provide an adjacent region of homology. Similarly, it may be desirable to target other genes to the region adjacent to *PMS2*. *JTV1* sequences can be used to flank

such other genes, providing one or more regions of homology. If insertion of other genes is desired between the *JTV1* and the *PMS2* sequences, again, this can be accomplished using the identified sequences as homology units for homologous recombination.

Examples

Example 1

Isolation and sequence analysis of the 5' end of *hPMS2*.

Purified DNA from P1 clone 53, previously determined to contain the *hPMS2* gene (Nicolaides, et.al., 1994), was digested with EcoRI and subcloned into the pBluescript vector (Stratagene). Clones containing the 5' region of *hPMS2* were identified by hybridization with primer A (Table 1) directed to exon 1. Restriction analysis of several positive clones showed them to be identical. The sequence of the relevant region of *hPMS2* was determined from both strands using ^{35}S α-dATP and Sequenase (USB).

Table 1. Primers used for *hPMS2*.

PRIMER NAME	STRAND	PRIMER SEQUENCE	POSITION*
A	sense	5'- cgggtgttgcatccatgg-3'	-14 - +4
B	sense	5'-gggtggagcacaacgtcg -3'	-110 - -93
C	sense	5'-ggtcacgacggagaccg-3'	-283 - -267
D	sense	5'-tgcaggtgggaagctccacacgg-3'	-414 - -392
E	sense	5'-tagctcctgccgtgcacg-3'	-448 - -431
F	sense	5'-cgctcctacctgcacgtg-3'	-487 - -470
G	antisense	5'-tagactcagtaccacctgc-3'	+90 - +107
H	sense	5'-tacagaacctgctaaggcc-3'	+24 - +42
I	antisense	5'-tttctactaactccttaccg-3'	+116 - +136
J	sense	5'-caaccatgagacacatcgc-3'	+2545 -
K	antisense	5'-aggttagtgaagactctgtc-3'	+2647 - +2666

* Relative to the presumptive initiating methionine in Figure 1.

Three clones were isolated, each containing an 8.5 kb EcoRI insert. Partial sequence analysis of one clone, pSMN, determined that it contained coding residues of *hPMS2* as well as sequences upstream of the previously designated codon 1. The presumptive initiating codon reported previously has been designated as nucleotide 1 in Figure 1. The sequence of *hPMS2* was extended 833 bp upstream of nucleotide 1. This sequence revealed an in-frame stop codon 321 nts upstream of the published initiator methionine, with no intervening methionines (Figure 1).

Example 2

Isolation of additional cDNA clones using *hPMS2* probes.

Two cDNA libraries were screened with a probe containing nt +24 to +136 of *hPMS2* generated by PCR using P1 clone 53 as template and the primers H and I (Table 1). A human small intestine random-primed cDNA library in λGT10 (Clontech) and a HeLa oligo-dT primed cDNA library in λZAPII (Stratagene) were screened as described except hybridizations were carried out at 68°C and filters were washed at 65°C for 0.5 hrs (Kinzler and Vogelstein, 1989). Following plaque purification, the EcoRI inserts from the small intestine library were subcloned into pBluescript vector, while the HeLa cDNA inserts were rescued as phagemids following the manufacturer's protocol (Stratagene).

One clone was isolated from the random-primed small intestine library, and this contained nt -14 to nt +1668 of *hPMS2*. Two clones were isolated from the oligo-dT primed HeLa cDNA library. The clones began at nt -53 and ended at either nts +2722 or +2749. The HeLa cDNA library was also screened with a 430 bp probe from the 5' genomic region of *hPMS2*, containing nt -414 to +16, generated by PCR from P1 clone 53 using primers D (Table 1) and O (Table 2). The same two clones were identified, as expected. However, twelve other overlapping clones were found and appeared to represent a different transcript, named *JTV1* (Figure 2). These twelve cDNAs were approximately 1.2 kb in length and were sequenced in their entirety. All twelve ended with a polyA tract (assumed to be the 3' end) and were identical for 1.2 kb upstream. The 5' ends were located within 38 bp of each other. Comparison with *hPMS2* indicated that *JTV1* was transcribed from the opposite strand.

Table 2. Primers used for *JTV-1* cDNA amplification.

PRIMER NAME	STRAND	PRIMER SEQUENCE	POSITION*
L	sense	5'-gttctgccatgccgatg-3'	-8 - +9
M	sense	5'-ggcctttggcacgcgctac-3'	-23 - -41
N	sense	5-accggactgcgttttcccg-3'	-111 - -129
O	sense	5'-tctcagctcgctccatgg-3'	-343 - -360
P	antisense	5'-gcagagacaggttagactc-3'	+139 - +157
Q	sense	5'-gctccttaagtgaattgccg-3'	+952 - +971
R	antisense	5'-tgacacttgacaactggcc-3'	+1068 - +1086

* Relative to the presumptive initiating methionine in Figure 2.

Example 3

JTV1.

The length of one clone representative of *JTV1* (pM23NNFL) was 1233 bp and encoded an open reading frame (ORF) of 936 bp (Figure 2). The first methionine within this ORF was designated codon 1 (Figure 2) and was preceded by an in-frame termination codon 66 bp upstream. This methionine had a reasonable match to the Kozak translation initiation consensus (Kozak, 1986). The 3' end contained a polyadenylation signal (AAUAAA) starting at nucleotide 1086 followed by a polyA tail. The transcript was predicted to encode a polypeptide of 312 amino acids, with a molecular weight of 34.5 kda. Searches of nucleotide and peptide sequence databases showed that this was a novel gene, with limited homology to the glutathione S-transferase gene family.

Example 4

Chromosomal Mapping of *JTV1*.

The *hPMS2* locus was previously mapped to chromosome 7p22 by FISH using P1 clone 53 (Nicolaides et.al., 1994). Because multiple *hPMS2*-related genes are located on the long arm of chromosome 7 and have conserved 5' regions (personal observation, Hori et.al., 1994), we confirmed the genomic localization of *JTV1* by PCR analysis of rodent-human somatic cell hybrid DNAs containing various regions of chromosome 7 (Scherer et.al., 1993; Powers et.al., 1993). PCR primers were chosen from the 3' untranslated region of *hPMS2* and *JTV1* and shown to amplify genomic DNA. *hPMS2* primers J and K yielded a 121 bp product and *JTV1* primers Q and R yielded a 134 bp product. PCR products for both genes were formed in those DNAs containing the 7p22 region: lines GM10791 (containing the entire human chromosome 7), NA11440 (Coriell Institute) (7p22 > 7pter) and Ru-Rag4-13 (7cen-7pter) (figure 3, lanes 1, 2, and 3). No products were observed in lines 4AF1/106/K015 (7cen-qter), GM05184.17 (7q21.2-qter), or 2068Rag22-2 (7q22-qter) (figure 3, lanes 4, 5, and 6).

Example 5

Analysis of the 5' Termini of *hPMS2* and *JTV1*.

The 5' termini of *hPMS2* transcripts were studied by standard cDNA cloning, RACE, and RT-PCR analyses. RNA was purified from tissues and cells using a guanidine isothiocyanate based method (Chomczynski and Sacchi, 1987). Reverse transcriptase-polymerase chain reaction (RT-PCR) was performed using randomly primed cDNA as template as described (Leach, et.al., 1993). RT-PCR of the 5' end of *hPMS2* was performed using a common antisense primer (I) and the sense primers (A-F) described in Table 1. RT-PCR mapping of the 5' end of *JTV1* was done using a common antisense primer P and the sense primers L-O as described in Table 2. RACE (rapid amplification of cDNA ends, Frohman, et.al., 1988) was performed on *hPMS2* using sequential antisense primers I and G (Table 1) following the manufacturer's protocol (Clontech). RACE analysis of *JTV1* was done using the antisense primer P (Table 2). Amplification products were cloned

into a T-tailed vector (InVitrogen) and sequenced using SP6 and T7 primers. Amplifications were done at 95°C for 30 sec, 56°C for 1.5 min., and 70°C for 1.5 min for 35 cycles. Reaction products were separated by electrophoresis in 6% nondenaturing polyacrylamide gels.

Figure 4 shows the sequence of the genomic region containing the transcriptional initiation sites of both *hPMS2* and *JTV1*, numbered as in Figure 1 with respect to *hPMS2*. The 5' ends of *hPMS2* cDNA clones are marked with arrowheads on the top strand. One clone began at nt -14, one at nt -24, and two at nt -53. RACE products were generated from adult brain, leukocyte, and placenta mRNA. Using an antisense primer corresponding to nt +116 to +136, multiple bands with approximately 160 to 191 bps were observed in addition to less intense bands of up to 550 bp. The sequence of four cloned RACE products demonstrated that, as expected, their 5' ends were located between nt -25 to -55. These data suggested that the majority of *hPMS2* transcripts initiated between nt -13 to -55, with a minority extending further upstream. This was confirmed by RT-PCR analysis using mRNA from HeLa cells as template. Robust RT-PCR products were amplified with sense primers whose 5' ends were at nt -14, -110, -283, and -414, (primers A, B, C, and D; Table 1) and an antisense primer corresponding to nt +90 to +107 (G). No PCR products were observed using sense primers whose 5' ends were at nt -448 or -487 (primers E and F). To ensure that primers E and F were not defective, successful amplification of genomic DNA was performed using these primers and an antisense primer (O) corresponding to nt -2 to +16.

The 5' termini of *JTV1* showed a heterogeneous pattern like that of *hPMS2*. The 5' ends of the 12 cDNA clones are indicated by arrowheads on the bottom strand in figure 4. They were located 73 to 113 nt 73 upstream of codon 1 of *JTV1*, which corresponded to nt -271 to -232 of *hPMS2*. RACE confirmed the cDNA results in that the majority of products generated using an antisense primer P corresponding to *JTV1* nt +157 were 230 to 270 bp. RT-PCR analysis was performed with antisense primer P and several sense primers (L-O) listed in Table 2. PCR products were found with sense primers whose 5' ends were at -8, -23,

and -111, (primers L,M, and N) but not with a sense primer O whose 5' end was at nt -360 with respect to *JTV1*, nt +1. The latter primer was not defective, as a genomic segment could be successfully amplified with it.

Transcripts of *hPMS2* had heterogeneous but collinear 5' termini, containing 11 to 415 nt of presumably untranslated sequence. The transcripts contained an in-frame stop codon upstream of the presumptive initiating methionines (Figure 1), making the originally described methionine the most likely translation initiator. Because no other upstream coding regions of *hPMS2* appeared to exist, the size discrepancy between that predicted from the *hPMS2* sequence and the 110 kDa *hPMS2* protein identified by Li and Modrich is likely due to post-transcriptional modifications or alternative internal exons.

Our results revealed that *hPMS2* overlaps with a novel gene, *JTV1*, transcribed from the opposite strand (Figure 4). This organization is similar to that of HUMDUG, a *mutS*-homolog found on human chromosome 5, and the dihydrofolate reductase (DHFR) gene (Fujii and Shimada, 1989). Both *hPMS2-JTV1* and HUMDUG-DHFR lie in a head to head arrangement, both genes are ubiquitously expressed, and both have multiple 5' termini. It has been hypothesized that DHFR and HUMDUG may be regulated via a bidirectional promoter, because a minor subset of the transcripts from the two genes overlap. The major transcripts of HUMDUG and DHFR, however, do not overlap, as is true for *hPMS2* and *JTV1*. It will be of interest to determine whether other mismatch repair genes are arranged in a head to head fashion with a contiguous gene and if *JTV1* is involved in DNA replication or repair.

Example 6

Expression of *hPMS2* and *JTV1*.

The expression of *hPMS2* and *JTV1* was analyzed in a variety of mRNA samples prepared from human tissues. RT-PCR was performed on cDNA templates derived from adult brain, leukocytes, kidney, large intestine, colon, salivary gland, lung, testes and prostate using primers J and K for *hPMS2* and

primers Q and R for *JTV1* (Tables 1 and 2). Both genes were expressed in all tissues tested (Figure 5).

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(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Kagan A., Sarah
(B) REGISTRATION NUMBER: 32,141
(C) REFERENCE/DOCKET NUMBER: 1107.49697

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 202-508-9100
(B) TELEFAX: 202-508-9299

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 384 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 46..384

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```
TTACCTGGTA CATCGGCATG GCAGAACCAA AGCAAAAGGG GGTAG CGC GTG CCA          54
                                                    Arg Val Pro
                                                      1

AAG GCC AAC GCT CAG AAA CCC TCA GAG GTC ACG ACG GAG ACC GGC CAC       102
Lys Ala Asn Ala Gln Lys Pro Ser Glu Val Thr Thr Glu Thr Gly His
  5                  10                  15

CTC CCT TCT GAC CCT GCT GCG GGC GTT CGG GAA AAC GCA GTC CGG TGT       150
Leu Pro Ser Asp Pro Ala Ala Gly Val Arg Glu Asn Ala Val Arg Cys
 20                  25                  30                  35

GCT CTG ATT GGC CCA GGC TCT TTG ACG TCA CGA AGT CGA CCT TTG ACA       198
Ala Leu Ile Gly Pro Gly Ser Leu Thr Ser Arg Ser Arg Pro Leu Thr
                 40                  45                  50

GAG CCA ATA GGC GAA AAG GAG AGA CGG GAA GTA TTT TTG CCG CCC CGC       246
Glu Pro Ile Gly Glu Lys Glu Arg Arg Glu Val Phe Leu Pro Pro Arg
             55                  60                  65

CCG GAA AGG GTG GAG CAC AAC GTC GAA AGC AGC CAA TGG GAG TTC AGG       294
Pro Glu Arg Val Glu His Asn Val Glu Ser Ser Gln Trp Glu Phe Arg
         70                  75                  80

AGG CGG AGC GCC TGT GGG AGC CCT GGA GGG AAC TTT CCC AGT CCC CGA       342
Arg Arg Ser Ala Cys Gly Ser Pro Gly Gly Asn Phe Pro Ser Pro Arg
  85                  90                  95

GGC GGA TCG GGT GTT GCA TCC ATG GAG CGA GCT GAG AGC TCG               384
Gly Gly Ser Gly Val Ala Ser Met Glu Arg Ala Glu Ser Ser
100                 105                 110
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 113 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
Arg Val Pro Lys Ala Asn Ala Gln Lys Pro Ser Glu Val Thr Thr Glu
 1               5                  10                  15

Thr Gly His Leu Pro Ser Asp Pro Ala Ala Gly Val Arg Glu Asn Ala
            20                  25                  30

Val Arg Cys Ala Leu Ile Gly Pro Gly Ser Leu Thr Ser Arg Ser Arg
        35                  40                  45

Pro Leu Thr Glu Pro Ile Gly Glu Lys Glu Arg Arg Glu Val Phe Leu
    50                  55                  60

Pro Pro Arg Pro Glu Arg Val Glu His Asn Val Glu Ser Ser Gln Trp
65                  70                  75                  80

Glu Phe Arg Arg Arg Ser Ala Cys Gly Ser Pro Gly Gly Asn Phe Pro
                85                  90                  95
```

```
Ser Pro Arg Gly Gly Ser Gly Val Ala Ser Met Glu Arg Ala Glu Ser
            100                 105                 110

Ser
```

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1233 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 114..1049

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

```
CCGAACGCCC GCAGCAGGGT CAGAAGGGAG GTGGCCGGTC TCCGTCGTGA CCTCTGACGG      60

TTTCTGAGCG TTGGCCTTTG GCACGCGCTA CACCCTTTTG CTTTGGTTCT GCC ATG      116
                                                           Met
                                                            1

CCG ATG TAC CAG GTA AAG CCC TAT CAC GGG GGC GGC GCG CCT CTC CGT      164
Pro Met Tyr Gln Val Lys Pro Tyr His Gly Gly Gly Ala Pro Leu Arg
              5                  10                  15

GTG GAG CTT CCC ACC TGC ATG TAC CGG CTC CCC AAC GTG CAC GGC AGG      212
Val Glu Leu Pro Thr Cys Met Tyr Arg Leu Pro Asn Val His Gly Arg
         20                  25                  30

AGC TAC GGC CCA GCG CCG GGC GCT GGC CAC GTG CAG GAA GAG TCT AAC      260
Ser Tyr Gly Pro Ala Pro Gly Ala Gly His Val Gln Glu Glu Ser Asn
     35                  40                  45

CTG TCT CTG CAA GCT CTT GAG TCC CGC CAA GAT GAT ATT TTA AAA CGT      308
Leu Ser Leu Gln Ala Leu Glu Ser Arg Gln Asp Asp Ile Leu Lys Arg
 50                  55                  60                  65

CTG TAT GAG TTG AAA GCT GCA GTT GAT GGC CTC TCC AAG ATG ATT CAA      356
Leu Tyr Glu Leu Lys Ala Ala Val Asp Gly Leu Ser Lys Met Ile Gln
                 70                  75                  80

ACA CCA GAT GCA GAC TTG GAT GTA ACC AAC ATA ATC CAA GCG GAT GAG      404
Thr Pro Asp Ala Asp Leu Asp Val Thr Asn Ile Ile Gln Ala Asp Glu
             85                  90                  95

CCC ACG ACT TTA ACC ACC AAT GCG CTG GAC TTG AAT TCA GTG CTT GGG      452
Pro Thr Thr Leu Thr Thr Asn Ala Leu Asp Leu Asn Ser Val Leu Gly
        100                 105                 110
```

```
AAG GAT TAC GGG GCG CTG AAA GAC ATC GTG ATC AAC GCA AAC CCG GCC          500
Lys Asp Tyr Gly Ala Leu Lys Asp Ile Val Ile Asn Ala Asn Pro Ala
    115                 120                 125

TCC CCT CCC CTC TCC CTG CTT GTG CTG CAC AGG CTG CTC TGT GAG CAC          548
Ser Pro Pro Leu Ser Leu Leu Val Leu His Arg Leu Leu Cys Glu His
130                 135                 140                 145

TTC AGG GTC CTG TCC ACG GTG CAC ACG CAC TCC TCG GTC AAG AGC GTG          596
Phe Arg Val Leu Ser Thr Val His Thr His Ser Ser Val Lys Ser Val
                150                 155                 160

CCT GAA AAC CTT CTC AAG TGC TTT GGA GAA CAG AAT AAA AAA CAG CCC          644
Pro Glu Asn Leu Leu Lys Cys Phe Gly Glu Gln Asn Lys Lys Gln Pro
            165                 170                 175

CGC CAA GAC TAT CAG CTG GGA TTC ACT TTA ATT TGG AAG AAT GTG CCG          692
Arg Gln Asp Tyr Gln Leu Gly Phe Thr Leu Ile Trp Lys Asn Val Pro
        180                 185                 190

AAG ACG CAG ATG AAA TTC AGC ATC CAG ACG ATG TGC CCC ATC GAA GGC          740
Lys Thr Gln Met Lys Phe Ser Ile Gln Thr Met Cys Pro Ile Glu Gly
    195                 200                 205

GAA GGG AAC ATT GCA CGT TTC TTG TTC TCT CTG TTT GGC CAG AAG CAT          788
Glu Gly Asn Ile Ala Arg Phe Leu Phe Ser Leu Phe Gly Gln Lys His
210                 215                 220                 225

AAT GCT GTC AAC GCA ACC CTT ATA GAT AGC TGG GTA GAT ATT GCG ATT          836
Asn Ala Val Asn Ala Thr Leu Ile Asp Ser Trp Val Asp Ile Ala Ile
                230                 235                 240

TTT CAG TTA AAA GAG GGA AGC AGT AAA GAA AAA GCC GCT GTT TTC CGC          884
Phe Gln Leu Lys Glu Gly Ser Ser Lys Glu Lys Ala Ala Val Phe Arg
            245                 250                 255

TCC ATG AAC TCT GCT CTT GGG AAG AGC CCT TGG CTC GCT GGG AAT GAA          932
Ser Met Asn Ser Ala Leu Gly Lys Ser Pro Trp Leu Ala Gly Asn Glu
        260                 265                 270

CTC ACC GTA GCA GAC GTG GTG CTG TGG TCT GTA CTC CAG CAG ATC GGA          980
Leu Thr Val Ala Asp Val Val Leu Trp Ser Val Leu Gln Gln Ile Gly
    275                 280                 285

GGC TGC AGT GTG ACA GTG CCA GCC AAT GTG CAG AGG TGG ATG AGG TCT         1028
Gly Cys Ser Val Thr Val Pro Ala Asn Val Gln Arg Trp Met Arg Ser
290                 295                 300                 305

TGT GAA AAC CTG GCT CCT TTT TAACACGGCC CTCAAGCTCC TTAAGTGAAT            1079
Cys Glu Asn Leu Ala Pro Phe
                310

TGCCGTAACT GATTTTAAAG GGTTTAGATT TTAAGAATGG TGCTCTTTCA TGCCTATTAT       1139

CAGTAAGGGG ACTTGTATTA GAGTCAGAGT CTTTTTATTT AGGCCAGTTG TCAAGTGTCA       1199

ATAAAAGCGC ATCATGTAAT TTAAAAAAAA AAAA                                   1233
```

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 312 amino acids

(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```
Met Pro Met Tyr Gln Val Lys Pro Tyr His Gly Gly Gly Ala Pro Leu
 1               5                  10                  15

Arg Val Glu Leu Pro Thr Cys Met Tyr Arg Leu Pro Asn Val His Gly
            20                  25                  30

Arg Ser Tyr Gly Pro Ala Pro Gly Ala Gly His Val Gln Glu Glu Ser
        35                  40                  45

Asn Leu Ser Leu Gln Ala Leu Glu Ser Arg Gln Asp Asp Ile Leu Lys
    50                  55                  60

Arg Leu Tyr Glu Leu Lys Ala Ala Val Asp Gly Leu Ser Lys Met Ile
65                  70                  75                  80

Gln Thr Pro Asp Ala Asp Leu Asp Val Thr Asn Ile Ile Gln Ala Asp
                85                  90                  95

Glu Pro Thr Thr Leu Thr Thr Asn Ala Leu Asp Leu Asn Ser Val Leu
            100                 105                 110

Gly Lys Asp Tyr Gly Ala Leu Lys Asp Ile Val Ile Asn Ala Asn Pro
        115                 120                 125

Ala Ser Pro Pro Leu Ser Leu Leu Val Leu His Arg Leu Leu Cys Glu
    130                 135                 140

His Phe Arg Val Leu Ser Thr Val His Thr His Ser Ser Val Lys Ser
145                 150                 155                 160

Val Pro Glu Asn Leu Leu Lys Cys Phe Gly Glu Gln Asn Lys Lys Gln
                165                 170                 175

Pro Arg Gln Asp Tyr Gln Leu Gly Phe Thr Leu Ile Trp Lys Asn Val
            180                 185                 190

Pro Lys Thr Gln Met Lys Phe Ser Ile Gln Thr Met Cys Pro Ile Glu
        195                 200                 205

Gly Glu Gly Asn Ile Ala Arg Phe Leu Phe Ser Leu Phe Gly Gln Lys
    210                 215                 220

His Asn Ala Val Asn Ala Thr Leu Ile Asp Ser Trp Val Asp Ile Ala
225                 230                 235                 240

Ile Phe Gln Leu Lys Glu Gly Ser Ser Lys Glu Lys Ala Ala Val Phe
                245                 250                 255

Arg Ser Met Asn Ser Ala Leu Gly Lys Ser Pro Trp Leu Ala Gly Asn
            260                 265                 270

Glu Leu Thr Val Ala Asp Val Val Leu Trp Ser Val Leu Gln Gln Ile
        275                 280                 285
```

Gly Gly Cys Ser Val Thr Val Pro Ala Asn Val Gln Arg Trp Met Arg
290 295 300

Ser Cys Glu Asn Leu Ala Pro Phe
305 310

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 900 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Homo sapiens

(ix) FEATURE:
(A) NAME/KEY: mRNA
(B) LOCATION: complement (1..900)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

ACACCCGGCC AATTTCTGTA TTTTTAGTAG AGACGAGGTT TTACCATGTT GGCCAGGCTA 60

GTCTCGAACT CCTGACCTCA GGTGATCCGC CCGCCTCGGC CTCCCAAAGT GCTGGGATTA 120

CAGGCGTGAG CCACGGCGCC CGGCCTGGAT AAATCTTTTA AAAGATAAAA GTCTGAGTGA 180

GTCCCTGGCC GGCCGGCACA GATGCCGGGG TGGGGCCGTG AACCGGTTGG GACGCGCTCG 240

CTCCGGCCTG GGGGACCCG GGCCAGCAGC CGGTCGCCGC GCGTGCGCAC TGGGCGGGGG 300

GCCCCGCGCT CCTACCTGCA CGTGGCCAGG CCCGGCGCTG GGCCGTAGCT CCTGCCGTGC 360

ACGTTGGGGA GCCGGTACAT GCAGGTGGGA AGCTCCACAC GGAGAGGCGC GCCGCCCCCG 420

TGATAGGGCT TTACCTGGTA CATCGGCATG GCAGAACCAA AGCAAAAGGG GGTAGCGCGT 480

GCCAAAGGCC AACGCTCAGA AACCGTCAGA GGTCACGACG GAGACCGGCC ACCTCCCTTC 540

TGACCCTGCT GCGGGCGTTC GGGAAAACGC AGTCCGGTGT GCTCTGATTG GCCCAGGCCC 600

TTTGACGTCA CGAAGTCGAC CTTTGACAGA GCCAATAGGC GAAAAGGAGA GACGGGAAGT 660

ATTTTTGCCC CCCCGCCCGG AAAGGGTGGA GCACAACGTC GAAAGCAGCC AATGGGAGTT 720

CAGGAGGCGC AGCGCCTGTG GGAGCCCTGG AGGGAACTTT CCCAGTCCCC GAGGCGGATC 780

GGGTGTTGCA TCCATCGAGC GAGCTGAGAG CTCGAGGTGA GCGGGGCTCG CAGTCTTCCG 840

GTGTCCCCTC TCGCGCGCCC TCTTTGAGAC CCACGGCATT CCAACCTCCC TGGAAATGGG 900

CLAIMS

1. A segment of cDNA consisting of the nucleotide sequence shown in Figure 2.

2. A vector comprising the segment of DNA of claim 1.

3. A host cell which comprises the vector of claim 2.

4. A composition consisting essentially of a protein consisting of the amino acid sequence shown in Figure 2.

5. A composition of protein *JTVI* as shown in Figure 1, wherein said composition is free of other human proteins.

6. A segment of cDNA which encodes the amino acid sequence of JTV1 protein shown in Figure 2.

7. A cDNA probe wherein said cDNA consists of between 15 and 1176 contiguous nucleotides of the sequence shown in SEQ ID NO:1.

```
                                                                  *  R
-370  TTA CCT GGT ACA TCG GCA TGG CAG AAC CAA AGC AAA AGG GGG TAG CGC  -322

       V  P  K  A  N  A  Q  K  P  S  E  V  T  T  E  T
-321  GTG CCA AAG GCC AAC GCT CAG AAA CCG TCA GAG GTC ACG ACG GAG ACC  -273

       G  H  L  P  S  D  P  A  A  G  V  R  E  N  A  V
-272  GGC CAC CTC CCT TCT GAC CCT GCT GCG GGC GTT CGG GAA AAC GCA GTC  -224

       R  C  A  L  I  G  P  G  S  L  T  S  R  S  R  P
-223  CGG TGT GCT CTG ATT GGC CCA GGC TCT TTG ACG TCA CGA AGT CGA CCT  -175

       L  T  E  P  I  G  E  K  E  R  R  E  V  F  L  P
-174  TTG ACA GAG CCA ATA GGC GAA AAG GAG AGA CGG GAA GTA TTT TTG CCG  -126

       P  R  P  E  R  V  E  H  N  V  E  S  S  Q  W  E
-125  CCC CGC CCG GAA AGG GTG GAG CAC AAC GTC GAA AGC AGC CAA TGG GAG   -77

       F  R  R  R  S  A  C  G  S  P  G  G  N  F  P  S
 -76  TTC AGG AGG CGG AGC GCC TGT GGG AGC CCT GGA GGG AAC TTT CCC AGT   -28

       P  R  G  G  S  G  V  A  S  M  E  R  A  E  S  S
 -27  CCC CGA GGC GGA TCG GGT GTT GCA TCC ATG GAG CGA GCT GAG AGC TCG   +21
```

Figure 1

```
-113  CC GAA CGC CCG CAG CAG GGT CAG AAG GGA GGT GGC CGG TCT CCG TCG TGA CCT CTG ACG GTT TCT GAG CGT TGG CCT TTG GCA   -31

   1                                                  M  P  M  Y  Q  V  K  P  T  H  G  G  G  A  P  L  R  V          18
 -30  CGC GCT ACA CCC TTT TGC TTT GGT TCT GCC ATG CCG ATG TAC CAG GTA AAG CCC TAT CAC GGG GGC GGC GCG CCT CTC CGT GTG   +54

  19  E  L  P  T  C  M  Y  R  L  P  N  V  N  G  R  S  Y  G  P  A  P  G  A  G  H  V  Q  E                          46
 +55  GAG CTT CCC ACC TGC ATG TAC CGG CTC CCC AAC GTG CAC GGC AGG AGC TAC GGC CCA GCG CCG GGC GCT GGC CAC GTG CAG GAA  +138

  47  E  S  H  L  S  L  Q  A  L  E  S  R  Q  D  D  I  L  K  R  L  Y  E  L  K  A  A  V  D                          74
+139  GAG TCT AAC CTG TCT CTG CAA GCT CTT GAG TCC CGC CAA GAT GAT ATT TTA AAA CGT CTG TAT GAG TTG AAA GCT GCA GTT GAT  +222

  75  Q  L  S  K  N  I  Q  T  P  D  A  D  L  D  V  T  N  I  I  Q  A  D  E  P  T  T  L  T                          102
+223  GGC CTC TCC AAG ATG ATT CAA ACA CCA GAT GCA GAC TTG GAT GTA ACC AAC ATA ATC CAA GCG GAT GAG CCC ACG ACT TTA ACC  +306

 103  T  N  A  L  D  L  N  S  V  L  Q  K  D  Y  Q  A  L  K  D  I  V  I  N  A  N  P  A  S                          130
+307  ACC AAT GCG CTG GAC TTG AAT TCA GTG CTT GGG AAG GAT TAC GGG GCG CTG AAA GAC ATC GTG ATC AAC GCA AAC CCG GCC TCC  +390

 131  P  P  L  S  L  L  V  L  N  R  L  L  C  E  N  F  R  V  L  S  T  V  N  T  N  S  S  V                          158
+391  CCT CCC CTC TCC CTG CTT GTG CTG CAC AGG CTG CTC TGT GAG CAC TTC AGG GTC CTG TCC ACG GTG CAC ACG CAC TCC TCG GTC  +474

 159  K  S  V  P  E  N  L  L  K  C  F  Q  E  Q  N  K  K  Q  P  R  Q  D  Y  Q  L  Q  F  T                          186
+475  AAG AGC GTG CCT GAA AAC CTT CTC AAG TGC TTT GGA GAA CAG AAT AAA AAA CAG CCC CGC CAA GAC TAT CAG CTG GGA TTC ACT  +558

 187  L  I  W  K  N  V  P  K  T  Q  N  K  F  S  I  Q  T  N  C  P  I  E  Q  E  Q  N  I  A                          214
+559  TTA ATT TGG AAG AAT GTG CCG AAG ACG CAG ATG AAA TTC AGC ATC CAG ACG ATG TGC CCC ATC GAA GGC GAA GGG AAC ATT GCA  +642

 215  R  F  L  F  S  L  F  Q  Q  K  N  N  A  V  N  A  T  L  I  D  S  W  V  D  I  A  I  F                          242
+643  CGT TTC TTG TTC TCT CTG TTT GGC CAG AAG CAT AAT GCT GTC AAC GCA ACC CTT ATA GAT AGC TGG GTA GAT ATT GCG ATT TTT  +726

 243  Q  L  K  E  Q  S  S  K  E  K  A  A  V  F  R  S  N  N  S  A  L  Q  K  S  P  U  L  A                          270
+727  CAG TTA AAA GAG GGA AGC AGT AAA GAA AAA GCC GCT GTT TTC CGC TCC ATG AAC TCT GCT CTT GGG AAG AGC CCT TGG CTC GCT  +810

 271  G  N  E  L  T  V  A  D  V  V  L  W  S  V  L  Q  Q  I  Q  Q  C  S  V  T  V  P  A  N                          298
+811  GGG AAT GAA CTC ACC GTA GCA GAC GTG GTG CTG TGG TCT GTA CTC CAG CAG ATC GGA GGC TGC AGT GTG ACA GTG CCA GCC AAT  +894

 299  V  Q  R  W  N  R  S  C  E  N  L  A  P  F                                                                      312
+895  GTG CAG AGG TGG ATG AGG TCT TGT GAA AAC CTG GCT CCT TTT TAA CAC GGC CCT CAA GCT CCT TAA GTG AAT TGC CGT AAC TGA  +978
+979  TTT TAA AGG GTT TAG ATT TTA AGA ATG GTG CTC TTT CAT GCC TAT TAT CAG TAA GGG GAC TTG TAT TAG AGT CAG AGT CTT TTT  +1063
+1063 ATT TAG GCC AGT TGT CAA GTG TCA ATA AAA GCG CAT CAT GTA ATT TAA AAA AAA AAA A                                    +1120
```

Figure 2

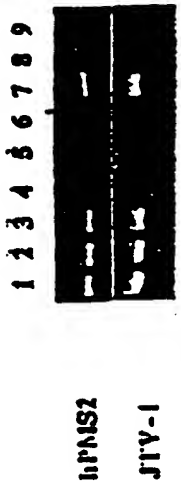

Figure 3

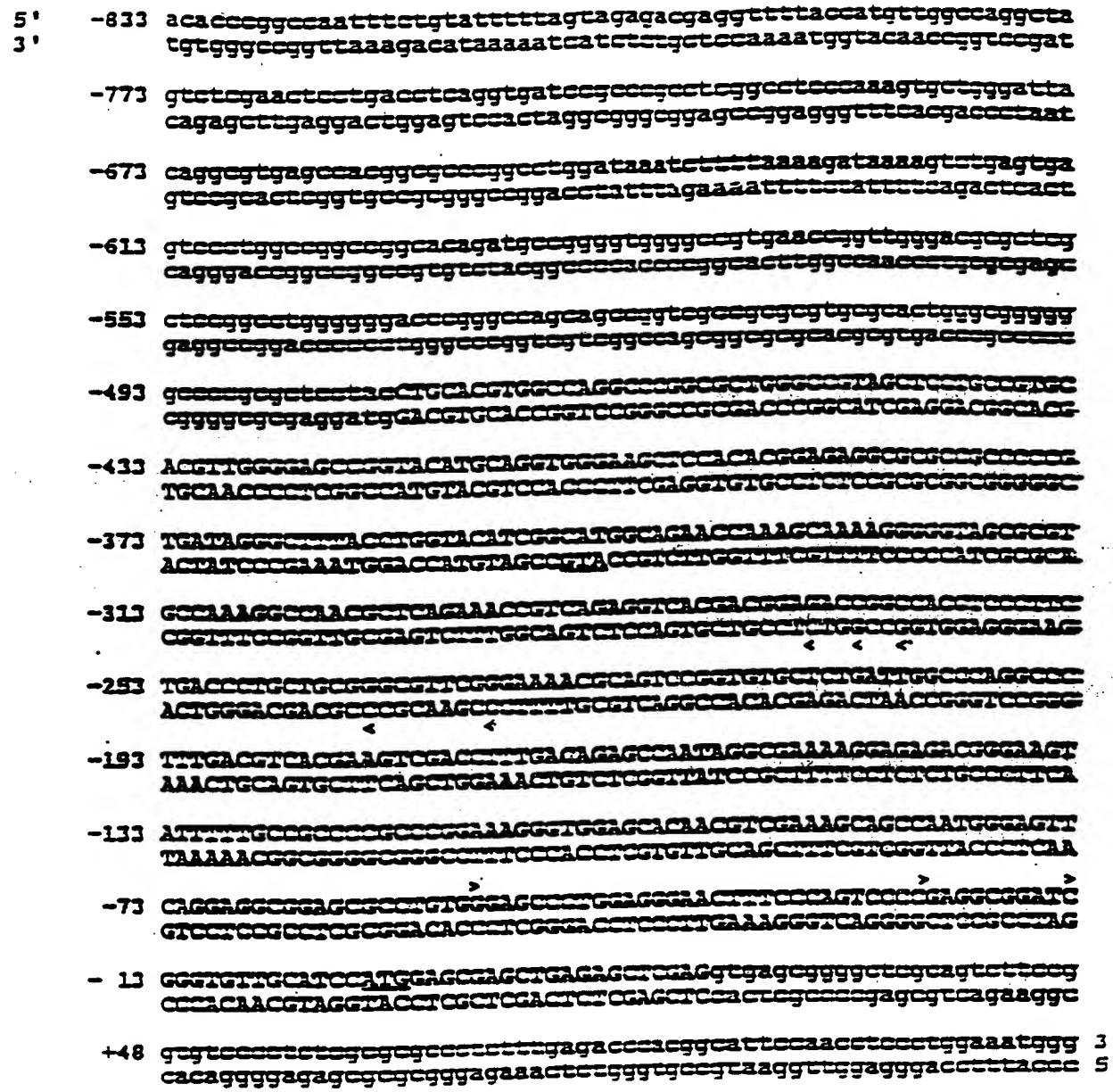

Figure 4

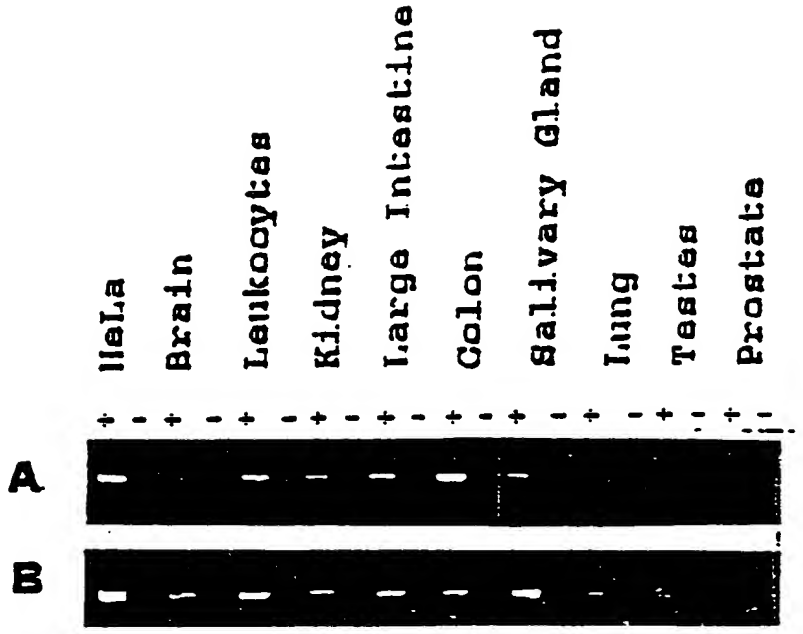
HeLa
Brain
Leukocytes
Kidney
Large Intestine
Colon
Salivary Gland
Lung
Testes
Prostate
+ - + - + - + - + - + - + - + - + - + -
A
B

Figure 5

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 96/13598

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C07K14/47 C12N1/21 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	GENOMICS, vol. 29, 20 September 1995, pages 329-334, XP000615435 NICOLAIDES N.C. ET AL.: "Analysis of the 5' region of PMS2 reveals heterogeneous transcripts and a novel overlapping gene." see the whole document ---	1-7
X	EMBL Database entry HS321180 Accession number R84321; 16 August 1992 HILLIER ET AL.:'The WashU-Merck EST Project.' XP002021622 see nucleotide sequence --- -/--	7

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 December 1996	06. 01. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mandl, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/13598

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EMBL Database entry HS461263 Accession number N26461 HILLIER L. ET AL.: 'The WashU-Merck EST project.' XP002021623 see nucleotide sequence ---	7
A	NATURE, vol. 371, 1 September 1994, pages 75-80, XP002021621 NICOLAIDES ET AL.: "Mutations of two PMS homologues in hereditary nonpolyposis colon cancer." cited in the application see the whole document -----	1-7

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FIG. 4B

```
-373 TGATAGGGCTTTACCTGGTACATCGGCATGGCAGAACCAAAGCAAAAGGGGGTAGCGCGT
     ACTATCCCGAAATGGACCATGTAGCCGTACCGTCTTGGTTTCGTTTTCCCCCATCGCGCA

-313 GCCAAAGGCCAACGCTCAGAAACCGTCAGAGGTCACGACGGAGACCGGCCACCTCCCTTC
     CGGTTTCCGGTTGCGAGTCTTTGGCAGTCTCCAGTGCTGCCTCTGGCCGGTGGAGGGAAG
                                                  <   <   <

-253 TGACCCTGCTGCGGGCGTTCGGGAAAACGCAGTCCGGTGTGCTCTGATTGGCCCAGGCCC
     ACTGGGACGACGCCCGCAAGCCCTTTTGCGTCAGGCCACACGAGACTAACCGGGTCCGGG
                  <       <

-193 TTTGACGTCACGAAGTCGACCTTTGACAGAGCCAATAGGCGAAAAGGAGAGACGGGAAGT
     AAACTGCAGTGCTTCAGCTGGAAACTGTCTCGGTTATCCGCTTTTCCTCTCTGCCCTTCA

-133 ATTTTTGCCGCCCCGCCCGGAAAGGGTGGAGCACAACGTCGAAAGCAGCCAATGGGAGTT
     TAAAAACGGCGGGGCGGGCCTTTCCCACCTCGTGTTGCAGCTTTCGTCGGTTACCCTCAA
              >                                   >           >

 -73 CAGGAGGCGGAGCGCCTGTGGGAGCCCTGGAGGGAACTTTCCCAGTCCCCGAGGCGGATC
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 - 13 GGGTGTTGCATCCATGGAGCGAGCTGAGAGCTCGAGgtgagcggggctcgcagtcttccg
      CCCACAACGTAGGTACCTCGCTCGACTCTCGAGCTCcactcgccccgagcgtcagaaggc

 +48 gtgtcccctctcgcgcgccctctttgagacccacggcattccaacctccctggaaatggg 3
     cacaggggagagcgcgcgggagaaactctgggtgccgtaaggttggagggacctttaccc 5
```

SUBSTITUTE SHEET (RULE 26)

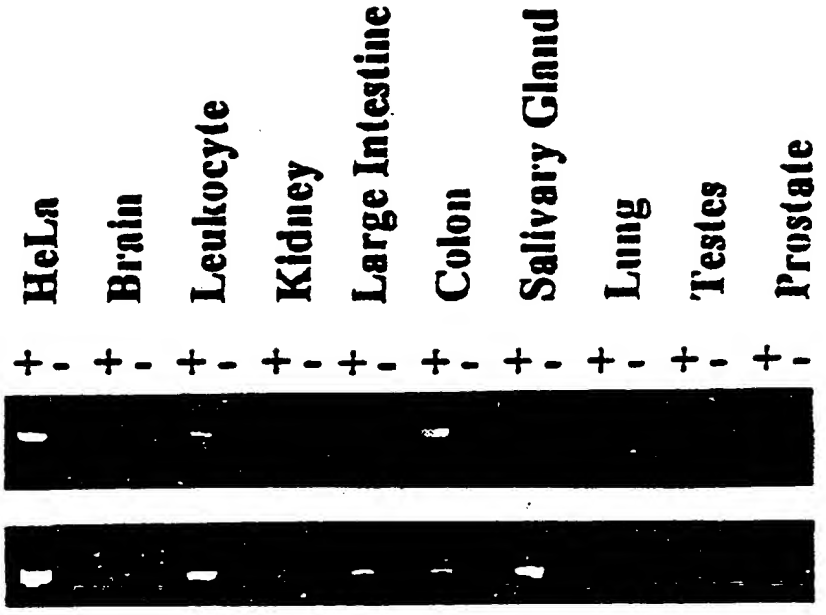
HeLa
Brain
Leukocyte
Kidney
Large Intestine
Colon
Salivary Gland
Lung
Testes
Prostate
+ - + - + - + - + - + - + - + - + - + -

FIG. 5A

FIG. 5B

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 96/13598

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C07K14/47 C12N1/21 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	GENOMICS, vol. 29, 20 September 1995, pages 329-334, XP000615435 NICOLAIDES N.C. ET AL.: "Analysis of the 5' region of PMS2 reveals heterogeneous transcripts and a novel overlapping gene." see the whole document ---	1-7
X	EMBL Database entry HS321180 Accession number R84321; 16 August 1992 HILLIER ET AL.:'The WashU-Merck EST Project.' XP002021622 see nucleotide sequence --- -/--	7

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 December 1996	06. 01. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Mandl, B

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/13598

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EMBL Database entry HS461263 Accession number N26461 HILLIER L. ET AL.: 'The WashU-Merck EST project.' XP002021623 see nucleotide sequence ---	7
A	NATURE, vol. 371, 1 September 1994, pages 75-80, XP002021621 NICOLAIDES ET AL.: "Mutations of two PMS homologues in hereditary nonpolyposis colon cancer." cited in the application see the whole document -----	1-7

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